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MEASURING SIDE EFFECTS OF PSYCHOPHARMACOLOGIC MEDICATION IN INDIVIDUALS WITH MENTAL RETARDATION AND DEVELOPMENTAL DISABILITIES

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To various degrees, psychopharmacologic medications are associated with side effects. Despite improvements in newer psychopharmacologic medication, monitoring for side effects remains important for individuals with mental retardation and developmental disabilities for a number of reasons, of which perhaps the most important is that many of these individuals cannot effectively verbally communicate the presence of side effects. This article reviews four basic areas. The first is classification of adverse drug reactions (ADRs) and basic terminology such as the difference between an ADR, side effect, adverse drug event, and adverse event. Second, the methods to approach ADRs are reviewed from an organizational, research, and applied individual perspective. Third, applied side effects rating scales are reviewed. Fourth, methods to determine the likelihood that a clinical manifestation indeed represents a side effect are reviewed. Although no one method will detect all side effects and although all methods generally detect more adverse events or clinical manifestations than actually turn out to be side effects, the material may allow for more structured monitoring of psychopharmacological medication side effects beyond general impression.

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An old joke begins by stating that a state legislature (pick your favorite) passes a law prohibiting people who are prescribed antihistamines from driving an automobile. It ends by noting that the law had to be rescinded because of problems during rush hour caused by major congestion.

Although this bit of humor uses antihistamine side effects (sedation) as the setup and the loss of antihistamine therapeutic effects (congestion) as the punch line, it succinctly captures an important concept when psychopharmacologic medication is prescribed; namely, every medication has benefits and risks, and intended therapeutic effects may be compromised or negated by secondary effects resulting from the intervention. The reality of this concept is conveyed by a meta-analysis of 39 prospective studies of hospitalized patients, which found that the overall incidence of serious adverse drug reactions (ADRs) was 6.7% or 2,216,000 patients [Lararou et al., 1998]. Psychopharmacologic medication accounts for approximately 3–6% of all side effects in hospital settings [Hogue et al., 1994; Johnston et al., 1990; Koch, 1990] and approximately 26% of all side effects in nursing home settings [Mahoney et al., 1991]. Specific to psychopharmacologic medication, 10% of 15,264 inpatients prescribed a psychopharmacologic medication displayed an ADR that led to the discontinuation of the psychopharmacologic medication [Grohmann et al., 1993]. It is logical to conclude that the 10% figure reported by Grohmann et al. [1993] would have been higher if it had included the patients who experienced an ADR requiring a dose reduction or auxiliary medication.

Even nonserious side effects of psychopharmacologic medication are quite important from a scientific and clinical perspective [Levine, 1990]. To varying degrees, side effects of psychopharmacologic medication may be associated with increased behavior problems [Kalachnik et al., 1995; Siris, 1985], misdiagnosis [Sovner and Hurley, 1982], medication noncompliance [Sleator et al., 1982; Van Putten, 1974], hospitalization [Fialkov and Hasley, 1984], and impaired cognitive function [Salzman et al., 1992]. Each of these can potentially interfere with learning and quality of life. It is doubtful whether any professional or multidisciplinary team member disagrees that monitoring for side effects is an important consideration when psychopharmacologic medication is prescribed for individuals with mental retardation or developmental disabilities (MRDD). However, efforts to implement such an activity beyond general impression may be difficult for several reasons. Other than ubiquitous economic, computer, staff, and logistical issues, reasons may include nonfamiliarity or confusion regarding the side effects area itself, the various methods and assessment instruments to detect or measure side effects, and the methods to determine the probability a clinical manifestation indeed represents a side effect.

The purpose of this article is to review side effects concepts and terminology, the methods and instruments to detect side effects, and the methods to determine a side effect is present. The premise is that formal standardized side effects monitoring is a critical activity when psychopharmacologic medication is prescribed for individuals with MRDD because many of these

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individuals cannot effectively verbally communicate the presence of side effects. This premise is supported by recommendations from both the Health Care Financing Administration (HCFA) and the Standards of Care Committee of the International Consensus Conference on Psychopharmacology [HCFA, 1996; Kalachnik et al., 1998]. These groups define a psychopharmacologic medication as any medication prescribed to stabilize or improve mood, mental status, or behavior.

Several qualifications regarding this article are necessary. First, although presented in the context of psychopharmacologic medication, the concepts apply to antiepileptic medication prescribed for individuals with MRDD. Second, the article makes no claim to be a comprehensive review of the literature. Third, emphasis is placed on applied methods. Although complex systems based on large databases, signal generation, and neural networks exist [Bate et al., 1998; Naranjo et al., 1992], most of these systems are beyond the scope of day-to-day applied activity. Fourth, except for the background section, ADRs and side effects will not be differentiated, and the term side effects will be used because this is generally used in the vernacular. Fifth, instruments to formally measure cognition are not reviewed. The reader interested in cognitive measures is referred to a review article that lists 87 different neuropsychological assessment instruments used in antiepileptic medication randomized controlled trials from 1966 to 1996 [Cochrane et al., 1998], a review of cognitive instruments to measure drug effects by Aman [1993], and several studies measuring cognitive and learning effects in children or individuals with either MRDD or autism prescribed medications such as haloperidol, naltrexone, and phenytoin [Aman et al., 1994; Anderson et al., 1989; Campbell et al., 1982; 1993; Sandman et al., 1990; Taylor et al., 1991].

BACKGROUND

Before turning to specific aspects of side effects measurement, a brief background of the terms and classifications used in the side effects literature is presented. Although interesting in and of itself, the intent is to provide the rationale for the organization of most clinical side effects instruments.

Perhaps the major point to remember is that the side effects literature is not uniform in its use of terminology. Different terms are used to describe the same phenomenon, the same term is defined differently, and differing classification systems exist. Indeed, the term "side effects" has been used in so many ways over the years that the Food and Drug Administration (FDA) has recommended, in relation to its postmarketing drug surveillance system, that the term not be used and especially not be equated with an adverse event or adverse drug reaction [FDA, 1995]. Great effort is being made by the World Health Organization (WHO) to harmonize pharmacovigilance or the field of drug safety monitoring [Edwards and Biriell, 1994], and these harmonized definitions will be emphasized. Table 1 presents a summary of the basic terms reviewed below.

Side Effect Definition and Relation to Other Terms

For day-to-day practical purposes (and for purposes of this article), the simplest definition of a side effect is a secondary effect of a drug that is usually undesirable and different from its therapeutic effect [Feldman and Quenzer, 1984].

Despite the propitious nature of this definition, it is critical to realize that what is loosely referred to as a side effect is but one category under the term

Table 1. Formal Terminology Encountered in Relation to Side Effects

Term	Definition	Comment
Adverse drug reaction (ADR)	". . . a response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function" [Edwards and Biriell, 1994, p. 94; FDA, 1995].	See Table 2 for types of ADRs. The terms "adverse reaction" and "adverse effects" generally equate with ADR.
Side effect	". . . any unintended effect of a pharmaceutical product occurring at doses normally used in man, which is related to the pharmaceutical properties of the drug at normal doses" [Edwards and Biriell, 1994, p. 94]	See Table 2. One type of ADR.
Adverse drug event (ADE)	An injury resulting from medical intervention related to a drug [Bates et al., 1995].	"Potential ADEs" are also a focus because from a systems perspective, these are considered errors that have the capacity to cause injury, but failed to do so only by chance or because they were intercepted.
Adverse event (AE)	". . . any untoward medical occurrence that may present during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with this treatment" [Edwards and Biriell, 1994, p. 94; FDA, 1995; 1997b; 1997c].	For purposes of FDA reporting, a "serious AE" is considered to be any event that is fatal, life-threatening, permanently or significantly disabling or incapacitating, requires or prolongs hospitalization, causes a congenital anomaly or birth defect, or requires intervention to prevent permanent impairment or damage [FDA, 1995; Goldman et al., 1996]. Some authors alternatively define "adverse event" to include an injury caused by *any* medical management. This definition includes injury not only from drug ADRs, but also from surgical mishaps, failure to use proper diagnostic tests, etc. [Brennan et al., 1991; Leape et al., 1991]. This use is closer to the concept of an ADE. Outside of the postmarketing surveillance perspective, "clinical manifestation" generally equates with AE. Clinical manifestations are abnormal signs, symptoms, or laboratory tests [Kramer et al., 1979] that may or may not turn out to be an ADR.

FDA = Food and Drug Administration.

adverse drug reaction (ADR) [Plaa and Willmore, 1995]. Although variations exist, Table 2 presents the generally accepted ADR categories. As shown in both Tables 1 and 2, side effects within the ADR definition are basically limited to known pharmacological effects of a drug at normal doses. As a definition, this excludes events such as poisoning after overdosing, abuse disorders, and actual malpractice [Bech et al., 1993; Edwards and Biriell, 1994].

Side effects and ADRs should not be confused with adverse drug event (ADE). ADE is a fairly recent term and only addresses more significant ADRs and events such as overdose [Bates et al., 1995]. ADEs revolve around the perspective that most drug-related injuries suffered by patients are preventable and are the endpoint of a series of events set in motion by faulty systems design of processes such as ordering or prescribing, transcribing, dispensing, and administration. Better systems design and earlier systems intervention should result in fewer errors and ADEs [Bates et al., 1995; Leape et al., 1995]. Paradoxically, ADE is a broader concept than ADR because it includes injury related to any aspect of drug use such as overdose, but is a narrower concept than ADR because it does not include the myriad of ADRs not causing actual injury.

The term adverse event (or experience) (AE) can best be understood in terms of the FDA. Reports by clinicians and health care providers are considered a critical first step within postmarketing drug surveillance and allow for the identification of rare or unexpected ADRs not identified during premarketing clinical trials. In the United States, this takes the form of the FDA's MedWatch program. After a drug is approved for marketing, the FDA is not interested in every ADE or ADR encountered because most of these have already been identified and taken into account within the process of FDA review, approval, and product labeling [Goldman et al., 1995]. Rather, what the FDA (and the WHO Collaborating Programme for International Drug Monitoring in other countries) is particularly interested in is unexpected or serious events related to a drug. Reporting of these events by healthcare providers is essentially voluntary, and the term "spontaneous reporting" is often used to describe this activity. The value of spontaneous reporting lies in generating signals of potential problems within complex statistical models, which, in turn, leads to hypothesis generation, further investigation, and possible action such as "Dear Health Professional" alert letters, requesting further manufacturer-sponsored postmarketing studies, labeling or packaging changes, and, in extreme cases, withdrawal of the product from the market [Goldman et al., 1996]. The FDA stresses to healthcare providers that the mere suspicion of a serious or unexpected event in relation to a drug, and not necessarily certainty of drug causality, is cause for reporting.

Viewed within this framework and from a practical day-to-day perspective, side effect measurement instruments basically list a series of signals. The presence of these signals (or their presence at a certain level) represents a clinical manifestation that may or may not represent a side effect. This leads to hypothesis generation, further investigation, and, if necessary, possible action in relation to the drug(s).

ADRs as Type A or Type B Reactions

ADRs have been classified into various subtypes over the years. In addition to the scheme presented in Table 2, a substantial portion of the literature categorizes ADRs as Type A or Type B reactions [Goldman et al., 1995; diShazo and Kemp, 1997; Pirmohamed et al., 1998; Vervloet and Durham, 1998]. Although not entirely satisfactory because of a degree of overlap, Type A and Type B reactions are viewed as an acceptable and straightforward way of looking at ADRs [Goldman et al., 1995].

Type A reactions are referred to as predictable events or reactions. They are also referred to as pharmacological or expected events or reactions. Type A reactions are common, account for most ADRs, and are caused by a drug's known pharmacological properties. Type A reactions usually are dose dependent, predictable, and reversible. They are rarely life-threatening, although incidence and morbidity may be high and significant

Table 2. Classification of Adverse Drug Reactions (ADRs)

Classification	Definition	Comment[a]
Allergic reaction	Reactions related to the immune system	Also referred to as *hypersensitivity* or *immunologic*. Considered a Type B reaction. *Example:* rash associated with carbamazepine or penicillin.
Idiosyncratic reaction	Uncharacteristic, unexpected, or unpredictable reaction dissimilar or unrelated to known pharmacological actions of the drug	Generally considered genetic and related to a metabolic or enzyme deficiency. May be difficult to distinguish from immune system response. Considered Type B reaction. Example: bone marrow depression from chloramphenicol.
Side effect	Undesirable, unintended, or unwanted reaction because of the known pharmacological effects of a drug	Limited to therapeutic doses. Considered a Type A reaction. *Example: fine hand tremor associated with lithium.*
Toxic reaction	Inordinate or exaggerated reaction to low or normal drug dose levels involving known (or extensions of the known) pharmacological properties of a drug	Confusing category. If, as used here, the emphasis is on a lowered threshold to normal pharmacological actions, *intolerance* is often used, and toxic reactions are considered Type B reactions. If, on the other hand, the emphasis is on an extreme response at supratherapeutic levels, *overdose* is often used, and toxic reactions are considered Type A reactions. Within the WHO ADR definition, the later issue is moot because only reactions at normal doses are considered an ADR. FDA MedWatch appears to classify a toxic reaction as Type A because of known pharmacology.
Adverse drug interactions	Reactions that are caused by drug–drug or drug–food interactions	Considered a Type A reaction. Example: bradycardia (slow heart beat) associated with co-administration of fluoxetine and propranolol.

WHO = World Health Organization, FDA = Food and Drug Administration.
[a]As explained further in the text, Type A reactions are predictable and common events related to a drug's known pharmacological properties that can occur in almost anyone. Type B reactions are unpredictable and uncommon events unrelated to a drug's known pharmacological properties that only occur in susceptible individuals.

disability a possibility. Type A reactions can occur in almost everyone and are readily recognized by most prescribers. In terms of Table 2, side effects, drug interactions, and toxic reactions are considered Type A reactions (although inclusion of toxic reactions may depend on how it is defined).

Type B reactions, on the other hand, are referred to as unpredictable events or reactions. They are also referred to as idiosyncratic or unexpected events or reactions. Type B reactions are uncommon and independent of a drug's known pharmacological properties. Type B reactions are not related to dose or route of administration and are rarely predictable or avoidable. They are considered the most serious and potentially life-threatening of ADR situations. Type B reactions tend to only occur in susceptible individuals and are a major cause of drug-induced disease. In terms of Table 2, allergic reactions and idiosyncratic reactions are considered Type B reactions (although toxic reactions may be included, depending on how it is defined).

Side Effects as Observable Signs and Symptoms

Although the term toxicity is used instead of ADR, one interesting model is that of Zbinden [1963]. Within this classification, biochemical toxicity is defined as drug-induced organ changes routinely detected by chemical methods and not accompanied by anatomical changes (e.g., agranulocytosis). Structural toxicity is defined as an actual alteration in the structure of the organ or tissue involved (e.g., lens opacities). Functional toxicity, which equates with the term side effects [Plaa and Willmore, 1995], is defined as pharmacological effects not necessary for the desired action of a drug (example: drooling).

This model is interesting in relation to applied side effects monitoring instruments because it stresses that the vast majority of ADRs are functional in nature and do not have specific laboratory tests to detect their presence. Additionally, the model notes that biochemical and structural toxicities often have functional signs (e.g., fever, pallor, fatigue, easy bruising, and sore throat may represent blood dyscrasias) that prompt physical examination or laboratory tests beyond the manufacturer's recommended schedule.

ADRs in Relation to Body Systems and Organ Systems

ADRs are commonly reported or categorized by body system or organ system. Some form of body or organ system often provides the organizational structure for listing clinical manifestations or side effects on rating scales.

Table 3 presents the WHO organ system to categorize ADRs [Alvarez-Requejo et al., 1998] and a body system used by the FDA [1997a]. Slight variations of these systems (e.g., autonomic, behavioral, central nervous system, dermatologic, neuropsychiatric, ocular, special senses, etc.) may occur in standard references such as *American Hospital Formulary Service* [1994], *Facts and Comparisons* [1995], *Physician's Desk Reference* [1998], and *United States Pharmacopeia* (USP) [1998]. For a more specific review of psychopharmacologic medication side effects in relation to body and organ systems, the interested reader is referred to Wilson et al. [1998].

ADRs in Relation to Neurotransmitters

Technically, ADRs are not categorized by neurotransmitter systems because ADRs include events beyond the known pharmacology of a drug. However, side effects (and drug interactions) may be categorized by neurotransmitter systems because, by definition, a drug's known pharmacology is involved.

Neurotransmitter systems have varying concentrations within the brain and other body organs, presynaptic reuptake mechanisms, and different presynaptic and postsynaptic receptor types and sites. A particular drug's side effects will depend on factors such as its specificity for a particular area and its affinity for and effect on a particular neurotransmitter, reuptake site, and receptor site. For a more in-depth review of neurotransmitters in relation to psychopharmacologic medications, the interested reader is referred to an excellent text by Stahl [1996]. Overall, because of the complex relationship between neurotransmitters, drugs, side effects, and drug interactions, applied side effects measurement instruments have not been organized along the lines of neurotransmitters.

Side Effects as a Function of Time

Side effects may be roughly viewed within two major temporal categories: early and late [Bech et al., 1993; Lingjaerde et al., 1987]. Although there is no absolute demarcation line between these two points, "early" is generally considered to be the first few weeks to the first few months after a medication is initiated [Bech et al., 1993]. Early side effects are also referred to as initial, immediate, short-term, or primary side effects. An example is sedation or headache after initiation of antidepressant medication. Many of the early side effects are transient; that is, they dissipate as a person's body adapts to the medication. As a general rule of thumb, the further removed from medication initiation or a dosage increase, the less likely a side effect will be transient. For example, weight gain over several weeks or months associated with valproic acid or olanzepine will not be transient. Although a rare exception may occur (e.g., tardive dyskinesia after limited neuroleptic exposure), early side effects dissipate on dose reduction or drug discontinuation.

Late side effects are also referred to as long-term, secondary, or tardive side effects. Classic examples of late side effects are tardive dyskinesia associated with neuroleptic medication and hypothyroidism associated with lithium. Late side effects, although not necessarily irreversible, are rarely transient. Some side effects such as neuroleptic malignant syndrome may occur either early or late in therapy.

To these two major temporal categories must be added a third category: withdrawal [Wilson et al., 1998]. Withdrawal side effects are also referred to as withdrawal reactions or withdrawal emergent effects. These side effects are associated with the reduction or discontinuation of a medication, especially abrupt discontinuation or large dosage reductions after longer-term use. Withdrawal side effects are usually transient and dissipate over several days to weeks. The classic examples of withdrawal reactions are withdrawal dyskinesia associated with

Table 3. Body and Organ Systems Used to Categorize Adverse Drug Reactions

Organ System (World Health Organization)[a]	Body System (Food and Drug Administration)[b]
Blood	Body as a whole
Cardiovascular	Cardiovascular
Gastrointestinal	Digestive
General	Hemic/lymphatic
Liver and biliary	Metabolic/nutritional
Local disorders	Musculoskeletal
Metabolic–endocrine	Nervous
Musculoskeletal	Respiratory
Neurological	Skin & appendages
Psychiatric	Special senses
Reproductive	Urogenital
Respiratory	
Skin and appendages	
Urinary	

[a]Alvarez-Requejo et al. [1998].
[b]FDA [1997a].

Table 4. Measurement of the Exacerbation of Agitation Caused by Carbamazepine Using Behavioral Methods*

Condition (days)	Rate of agitation per day using 30-min time sample (%)	Drugs and dose (mg/d)[a]			
		CBZ	HAL	LZP	AMD
1 (44)	19.1	2,000	1.5	1	0
2 (29)	16.8	1,900	1.5	1	0
3 (63)	23.6	1,800–1,600	1.5	1	0
4 (49)	23.2	1,400–1,000	1.5	1	0
5 (26)	7.6	800–600	1.5	1	0
6 (28)	7.7	400–200	1.5	1	0
7 (50)	2.0	0	1.5	1	0
8 (18)	1.6	0	1.5	0.5–0	0
9 (46)	11.3	0	1.5–1.25–1.5	0	200
10 (91)	2.1	0	1.5	0	0

*From Kalachnik et al. [1995].
[a]CBZ = carbamazepine, HAL = haloperidol, LZP = lorazepam, AMD = amantadine. All CBZ serum levels are within or below therapeutic range.

neuroleptic medication and agitation, tremor, and sweating associated with benzodiazepines.

METHODS TO DETECT AND MEASURE SIDE EFFECTS

Methods to detect and measure side effects may be approached from three different perspectives: organizational, clinical research, and applied individual. Although all strive for better care of patients and the detection and measurement of side effects, each has a slightly different focus.

From an organization perspective, hospitals and other care settings such as Veterans Administration Medical Centers approach side effects detection and measurement in terms of formal screening programs. Four basic methods may be involved [Hogue et al., 1994; Johnston et al., 1990, Koch, 1990; Mahoney et al., 1991]. Retrospective methods review clients' charts for entries that might represent a side effect. Laboratory methods screen laboratory reports for abnormal values. Alerting order methods screen prescriber orders for: a) antidotes or "tracer" drugs used for the treatment of suspected side effects and b) medication discontinuation orders and laboratory test orders that indicate a side effect may have occurred. Spontaneous (volunteer) reporting methods involve adverse event reporting by staff. No one method is perfect, and none will detect all side effects [Jones, 1979; Goldman et al., 1996]. Most organizations for accreditation purposes use a combination of the four methods, which is referred to as concurrent screening programs and usually coordinated by the Pharmacy and Therapeutics Committee. The focus is on active systems to continually minimize side effects. For example, inquiry and analysis resulting from tracer drug indicators may reveal that a drug with a high side effects profile is being used. Education about alternative but equally effective drugs may be called for as an active systems intervention which, if effective, should be reflected in fewer side effects and a lower number of tracer drug alerts in relation to that particular area.

Research involving psychopharmacologic medication approaches side effect detection and measurement from a protocol assessment model. Five basic methods may be involved [Campbell and Palij, 1985; Zametkin and Yamada, 1993]. Rating scales and checklists list specific side effects within a present–absent or a quasiobjective numerical indicator format (e.g., 0 = not present, 1 = mild, 2 = mild, etc.). Electrophysiological methods involve tests such as electroencephalograms or electrocardiograms. Physical and neurological examination involves specific examination procedures (e.g., neurological examination for subtle signs). Laboratory methods check drug serum levels and other body biochemistry. Various other devises involve a wide array of cognitive measures and electronic devices (e.g., stabilimetric cushion, which measures wiggling or movement while sitting and performing a task). Here again, no one method will detect all side effects, and most clinical research uses some combination of these methods. The focus usually is to determine the extent of side effects within a specific group using a specific drug. To improve the quality of data, Levine [1990] outlined three areas of methodology that should be addressed in these types of studies to improve the uniformity of side effects data: a) the method by which a rater or examiner obtains information (e.g., spontaneous reporting by the patient or staff, general inquiry, or detailed checklists or scales), b) the extent of information collected about an event to attribute cause and degree of clinical impact (e.g., severity, onset, duration, pattern such as isolated or continuing, other contributing factors such as illness), and c) the timeframe involved (e.g., does the inquiry refer to the past week, the period since the last inquiry, or to the present moment of the inquiry? Are baseline periods equal to the drug trial periods?).

Applied individual methods approach side effects measurement from a behavioral perspective and use measurement techniques from behavioral psychology [Hanzel et al., 1992; Mayhew et al., 1992; Kalachnik et al., 1995]. The basic measures are frequency count, duration recording, time sample, interval recording, and permanent products. A specific behavior (target) displayed by an individual is measured across drug or dose conditions and rates are compared. The focus of this method is generally limited to behavioral side effects or behavioral exacerbation of a preexisting challenging behavior (although a well-focused specific item such as lack of blinking could be measured by counting the number of blinks during several 1-minute periods, computing the average, and comparing rates after a specific drug or dose change). As an example, Table 4 presents a case involving a 30-minute time sample; that is, the client was spot checked once every 30 minutes to determine whether a specific behavior was present. Carbamazepine, which was prescribed for agitation, was hypothesized to be exacerbating agitation, and a step-by-step plan was developed to test this hypothesis. The client's agitation significantly decreased, which confirmed the hypothesis. Lorazepam (Ativan), also prescribed for agitation, was additionally able to be discontinued. This later event points out a potential problem with behavioral side effects; namely, a psychopharmacological medication may in some cases be inadvertently prescribed or prescribed at higher doses than necessary to treat behavioral side effects or behavioral exacerbation from the first medication [Hanzel et al., 1992]. Although more labor-intensive, behavioral measurement methods provide a unique method from which to approach this issue.

To summarize, numerous methods exist to approach the measurement of side effects of psychopharmacologic medication. Indeed, several methods may be simultaneously occurring at different levels. For example, the prescriber may be conducting laboratory tests per package

insert recommendations, the pharmacy may be screening alert orders and laboratory tests, staff may be providing spontaneous reports of serious adverse events, nurses may be conducting periodic checks with rating scales to better detect side effects, and a particular multidisciplinary team may be using behavioral methods for a particular individual's problem hypothesized to represent behavior side effects. Technically, it is important to recognize that whereas organizational methods focus on ADRs, applied individual methods are generally limited to side effects. Although clinical research methods focus on ADRs, rating scale methods are usually limited to side effects and drug interactions.

SIDE EFFECTS RATING SCALES

In terms of direct interaction with clients, the three common methods of detecting side effects are open-ended questioning (e.g., "have you had any problems in the past week?"), systematic assessment through a checklist of signs and symptoms (e.g., rating scale), and spontaneous reporting (by the client) [Corso et al., 1992]. Compared to spontaneous reporting alone, side effect detection approximately doubles when systematic inquiry methods such as rating scales are used with spontaneous reporting [Corso et al., 1992; Herranz et al., 1982]. Although spontaneous reporting by nonverbal clients is problematic, Lingjaerde et al. [1987] note that even verbal clients do not always report or complain about even important side effects.

Ongoing vigilance and spontaneous reporting by staff of any unusual event is important because side effects can occur at any time, and side effect rating scales or checklists are only intended for periodic use. The value of systematic inquiry with side effects rating scales is not necessarily in detecting serious events, but rather in detecting mild to moderate problems that would normally lead to a change in clinical management. Rabkin et al. [1992] found that specific side effect inquiry methods detected approximately 40% more mild to moderate events that led to a clinical change than did general inquiry.

Side effect rating scales may be broken into three types. The first type is medication-specific side effect scales and is what Campbell and Palij [1985] refer to as checklists. As the name suggests, these scales list side effects specific to a drug or a drug class. Although a few standardized medication-specific scales exist in the literature (e.g., stimulants [Barkley et al., 1990]), most are created from standard pharmaceutical references. The major advantage of these scales is that they are limited to the medication the individual is prescribed. For example, if lithium for bipolar disorder is prescribed, it makes sense to have a scale specific for lithium or antimania medication. Such a scale is especially advantageous for the clinic or organization that primarily serves clients prescribed a particular medication or medication class. The major disadvantage of these scales occurs when more than one drug is prescribed, when numerous drug changes occur, and when a variety of medications are prescribed for a variety of clients. Checklists multiply, interactive effects may be overlooked, and confusion may result from switching from checklist to checklist.

The second type is comprehensive or general-purpose side effects scales. These are longer instruments that list side effects for and across numerous drug classes. These scales generally take one of two approaches. They either list specific signs and symptoms (e.g., rigidity, oculogyric crisis, torticollis) or specific side effects (e.g., dystonia). Comprehensive side effects scales tend to be organized along some type of body-area, organ-system, or similar cluster, but differ in depth of coverage. That is, some are designed to be inclusive of all medications while others are designed for only psychopharmacologic medication. Some address items from a present-absent format while others rate the intensity of an item (e.g., minimal, mild, moderate, severe). The advantage of these scales is that they can be used across a variety of medications and clients which minimizes confusion and paper. The disadvantage is that the scale may not address a specific side effect in enough detail (e.g., tardive dyskinesia), or, alternatively, may list too many side effects which do not apply to the medication a particular individual is prescribed.

The third type is side effect-specific scales. These scales address an individual side effect or clinical situation in greater detail. Although a side effect such as drooling is not complex, a side effect such as tardive dyskinesia (TD) or extrapyramidal side effects (EPSE) may be composed of various signs, which can vary from client to client. Specialized situations such as medication withdrawal may also have a specific subset of signs and symptoms of interest. The advantage of these scales is that an in-depth detailed assessment is provided. These scales tend to be strong in terms of psychometrics and often provide an "indicator" score prompting further clinical inquiry. The disadvantage is that the scales are limited to a specific side effect or situation. The provider is forced to use an additional side effects scale or checklist for other side effects, which increases paperwork.

Table 5 provides a list of a number of side effects rating scales. Five scales—one because of its comprehensiveness and four because of development in relation to individuals with MRDD—are of particular interest. This is not to imply that the other scales cannot be used with individuals with MRDD in terms of either applied monitoring or research. Aman et al. [1991], for example, used the Dosage and Treatment Emergent Symptoms Scale (DOTES) to assess side effects of methylphenidate and thioridazine in individuals with MDDD.

The Adverse Drug Reaction Detection Questionnaire [Corso et al., 1992] is the most comprehensive scale on the list because the authors systematically organized more than 600 signs and symptoms from the 1990 *United States Pharmacopeia* into 24 body-system questions. The questionnaire uses a present–absent format and presents signs and symptoms in layperson's language. Although at first glance overwhelming, many items are subsumed under a primary item. For example, if "changes in skin color" in the skin area is negative, the item is skipped, and one moves to the next item. However, if the item is positive, one is directed to a sublisting of 36 types of skin color changes intended to pinpoint the exact nature of the change for purposes of determining associations with specific drugs.

The Matson Evaluation of Drug Side Effects Scale [Matson et al., 1998; Matson and Baglio, 1998] presents 90 items organized into nine body area and side effect classifications: (1) cardiovascular and hematologic; (2) gastrointestinal; (3) endocrine and genitourinary; (4) ears, eyes, nose, and throat; (5) skin, allergies, and temperature; (6) central nervous system (CNS) general; (7) CNS dystonia; (8) CNS parkinsonism and dyskinesia; and (9) CNS behavioral and akathisia. Items are presented in layperson's language and scored on two dimensions. One score is based on severity (no problem, mild or moderate, severe), whereas another is based on duration (less than 1 month, between 1 and 12 months, more than 12 months). Point totals are computed for each body area based upon

Table 5. Various Side Effects Assessment Scales

	Brief description
Type: Comprehensive	
Adverse Drug Reaction Detection Scale (ADRDS) [Corso et al., 1992]	600-item plus scale organized in 24 body areas.
Dosage Record & Treatment Emergent Symptom Scale (DOTES) [NIMH, 1985b]	33-item scale organized in 8 areas. Standard NIMH instrument used in psychopharmacology drug clinical research trials.
Interval & Final Rating Sheets on Side Effects [Gofman, 1972–1973]	63-item parental version not organized into areas. Physician interview version consists of 56 questions, physician examination consists of 43 items, and physician conclusion consists of 26 items.
Matson Evaluation of Drug Side Effects Scale (MEDS) [Matson et al., 1998; Matson and Baglio, 1998]	90-item scale organized by nine areas. Psychometric data provided in relation to individuals with MRDD.
Monitoring of Side Effects Scale (MOSES) [Kalachnik, 1988]	73-item (original version) organized by 10 body areas typical of clinical examination. Scoring levels adapted from DOTES. Revised version has 81 items.
Scandinavian Society of Psychopharmacology Side Effects Rating Scale (UKU) [Lingjaerde et al., 1987]	56-item scale organized into four areas. Extensive psychometrics and full manual.
Subjective Treatment For Treatment Emergent Symptoms Scale (STESS) [NIMH, 1985c]	32-item scale not organized by body areas.
Systematic Assessment for Treatment Emergent Effects (SAFTEE) [Levine and Schooler, 1986]	77-item scale organized into 13 body areas. Includes specific inquiry and general inquiry versions. Psychometrics provided. Excellent source for questioning techniques and related events.
Treatment Emergent Symptoms Scale (TESS) [NIMH, 1985d]	Open-ended fill-in scale intended for use with DOTES.
Type: Medication Specific	
	Brief description
Antiepileptic Systemic & Neurotoxicity Scales [Cramer et al., 1983]	System using scales for seizure frequency and severity, systemic toxicity, and neurotoxicity. Scale scores are combined for composite score.
Liverpool University Neuroleptic Side Effects Rating Scale (LUNSERS) [Day et al., 1995]	51-item scale including 10 "red herring" items. Psychometrics provided.
Naltrexone Side Effects Scale [Sandman et al., 1998]	10-item scale using 1 (not present) through 5 (constant characteristic) scoring system.
Side Effects of Antiepileptic Drugs Scale [Carpay et al., 1996]	20-item scale in layperson's language specific to antiepileptic medication. Psychometrics provided. Study size of 81 children included 37 children with MRDD.
Stimulant Drug Side Effects Scale [Barkley et al., 1990]	17-item rating scale specific to stimulant medication.
Type: Side Effects Specific	
	Brief description
Abnormal Involuntary Movement Scale (AIMS) [NIMH, 1985a]	7-item tardive dyskinesia (TD) scale organized into three body areas. Three additional items address incapacitation, global severity, and patient awareness. Well-recognized and original published TD scale.
Abnormal Involuntary Movement Scale For Recognizing Acute Extrapyramidal System Effects (AIMS-EPS) [Borison, 1985]	13-item EPSE scale. Items well defined in layperson's language.
Akathisia Ratings of Movement Scale (ARMS) [Bodfish et al., 1997]	10-item akathisia scale organized in three areas. Psychometrics for mental retardation and "indicator" score.
Barnes Akathisia Rating Scale (BARS) [Barnes, 1989]	3-item akathisia scale. Scoring levels for each item vary depending on definition. Descriptions provided basis for ARMS.
Dyskinesia Identification System Condensed User Scale (DISCUS) [Sprague and Kalachnik, 1991]	15-item TD scale organized into seven body areas. Extensive psychometrics for individuals with MRDD and "indicator" score tested for sensitivity and selectivity. Manual and training program.
Extrapyramidal Symptom Rating Scale (ESRS) [Chouinard et al., 1980]	Scale including patient questionnaire for pseudoparkinsonism (9 items), physician examination for pseudoparkinsonism (8 items), and TD (5 items).
Hillside Akathisia Scale [Fleischhacker et al., 1991]	5-item akathisia scale organized into subjective and objective areas.
Neurological Rating Scale (also called Simpson-Angus) [Simpson and Angus, 1970]	10-item EPSE scale. Scoring levels specifically defined for each item.
Tardive Dyskinesia Rating Scale (TDRS) [Simpson et al., 1979]	34-item TD scale.
Texas Research Institute for Mental Sciences Tardive Dyskinesia Scale (TRIMS) [Smith et al., 1983]	26-item TD and pseudoparkinsonism scale.
Withdrawal Emergent Symptoms Checklist (WES) [Engelhardt, 1974]	13-item scale organized into five areas specific to medication discontinuation.

NIMH = National Institute of Mental Health, MRDD = mental retardation and developmental disabilities, EPSE = extrapyramidal side effects

these two scores. Reliability coefficients are reported based upon interviews with significant staff working with individuals prescribed medication. Other than the DISCUS and ARMS, this is one of the few scales which provides psychometric data in relation to individuals with MRDD.

The Monitoring of Side Effects Scale (MOSES) [Kalachnik and Nord, 1985; Kalachnik, 1988] presents 73 items in layperson's language organized into nine body areas representing a typical physical examination as recommended by a task force consisting of psychiatrists, physicians, clinical pharmacists, and nurses. MOSES was developed based on review of psychopharmacologic and antiepileptic medication drug sections of standard pharmaceutical references such as *American Hospital Formulary Service* and *Facts and Comparisons* and existing side effects rating scales at the time, and implemented systemwide in Minnesota as part of a

Table 6. Monitoring of Side Effects Scale (MOSES) Items*

Ears/eyes/head
1. **Blink rate: decreased**
2. **Eyes: rapid vert./horiz.**
3. **Eyes: rolled up**
4. **Face: no expression/masked**
5. **Tics/grimace**
6. Blurred/double vision
7. Ear ringing
8. Headache

Mouth
9. **Drooling**
10. **Dry mouth**
11. **Gum growth**
12. **Mouth/tongue movement**
13. Speech: slurred/difficult/slow

Nose/throat/chest
14. **Breast: Discharge**
15. **Breast: Swelling**
16. **Labored Breathing**
17. **Nasal congestion/runny nose**
18. **Sore throat/redness**
19. **Swallowing: difficult**

Gastrointestinal
20. **Vomiting**/nausea
21. Abdominal pain
22. Appetite: decreased
23. Appetite: increased
24. Constipation
25. Diarrhea
26. Flatulence
27. Taste abnormality: metallic, etc.
28. Thirst: increased

Musculoskeletal/Neurological
29. **Arm swing: decreased**
30. **Contortions/neck—back arching**
31. **Gait: imbalance/unsteady**
32. **Gait: shuffling**
33. **Limb jerking/writhing**
34. **Movement: slowed/lack of**
35. **Pill rolling**
36. **Restlessness/pacing/can't sit still**
37. **Rigidity**/complaints of muscle pain
38. **Tremor/shakiness**
39. Complaints of jitteriness/jumpiness
40. Fainting/dizziness/on standing
41. Seizures: increased
42. Tingling/numbness
43. Weakness/fatigue

Skin
44. **Acne**
45. **Bruising: easy/pronounced**
46. **Color: blue/coldness**
47. **Color: flushing/warm to touch**
48. **Color: pale/pallor**
49. **Color: yellow**
50. **Dry/itchy**
51. **Edema**
52. **Hair: abnormal growth**
53. **Hair: loss**
54. **Rash/hives**
55. **Sunburns/redness**
56. **Sweating: decreased**
57. **Sweating: increased**
58. Chills

Urinary/Genital
59. Menstruation: absent/irregular
60. Sexual: activity decreased
61. Sexual: activity increased
62. Sexual: erection inability
63. Sexual: continual erection
64. Sexual: orgasm difficult
65. Urinary retention
66. Urination: decreased
67. Urination: difficult/painful
68. Urination: increased
69. Urination: nocturnal/enuresis

Psychological
70. **Agitation**
71. **Confusion**
72. **Crying**/feelings of sadness
73. Drowsiness/lethargy/**sedation**
74. **Irritability**
75. **Withdrawn**
76. Attention/concentration difficulty
77. Morning "hangover"
78. Nightmares/vivid dreams
79. Perceptual: hallucinations/delusions
80. Sleep: excessive
81. Sleep: insomnia

Measures
Temperature:
Pulse:
Blood Pressure:

Other (list)

*Bold items indicate items typically observable during examination. Nonbold items typically indicate client needs to be verbal to answer inquiry. If nonverbal, records need to be reviewed or staff or family questioned. This is an updated version of MOSES items that differs from the earlier Kalachnik and Nord [1985] and Kalachnik [1988] versions. Items are scored on a 0–4 basis. *0: Not present* (the item is not observable or is within the range of normal). *1: Minimal* (the item is difficult to detect. It is questionable if the item is in the upper range of normal. The client does not notice or comment on the item. Alternatively, the item may occur a couple of times in a noticeable but short, nonintense, and nonrepetitive manner). *2: Mild* (the item is present, but does not hinder the client's normal functioning; i.e., his or her level at pretreatment. Although client is not in extreme discomfort, it is an annoyance to the client or may progress to future severity and problems if ignored. Alternatively, the item may be continuously displayed in a nonintense manner or may "come and go" several times in a noticeable but nonintense manner). *3: Moderate* (the item is present and produces some degree of impairment to functioning, but is not hazardous to health. Rather, it is uncomfortable and/or embarrassing to the client. Alternatively, the item may be displayed in a semi-intense manner "more often than not.") *4: Severe* (the item is a definite hazard to well-being. There is significant impairment of functioning or incapacitation. Alternatively, the item may be displayed in an intense and continuous or nearly continuous manner). *NA: Not assessable* (the client will not cooperate with the item, appropriate data are not available, etc).

Table 7. DISCUS and ARMS Items*

DISCUS[a,b]	ARMS[a,c]
Facial	*Sitting*
1. Tics	1. Fidgety arms/hands
2. Grimaces	2. Fidgety legs/feet
Ocular	3. Shifting positions
3. Blinking	4. Inability to remain seated
Oral	*Standing*
4. Chewing/lip smacking	5. Shifting weight foot-to-foot
5. Puckering/sucking/thrusting lower lip	6. Marching on the spot
Lingual	7. Inability to remain standing
6. Tongue thrusting/tongue in cheek	*Lying*
7. Tonic tongue	8. Fidgety legs/feet
8. Tongue tremor	9. Truncal movements
9. Athetoid/myokymic/lateral tongue	10. Inability to remain lying
Head/neck/trunk	
10. Retrocollis/torticollis	
11. Shoulder/hip torsion	
Upper limb	
12. Athetoid/myokymic finger/wrist/arm	
13. Pill rolling	
Lower limb	
14. Ankle flexion/foot tapping	
15. Toe movement	

*DISCUS = Dyskinesia Identification System Condensed User Scale, ARMS = Akathisia Ratings of Movement Scale.
[a]Items on both scales are scored on a 0–4 basis. *0: Not present* (movements not observed or some movements observed but not considered abnormal). *1: Minimal* (abnormal movements are difficult to detect or movements are easy to detect but only occur once or twice in a short, nonrepetitive manner). *2: Mild* (abnormal movements occur infrequently and are easy to detect). *3: Moderate* (abnormal movements occur frequently and are easy to detect). *4: Severe* (abnormal movements occur almost continuously and are easy to detect). *NA: Not assessable* (an assessment for an item is not able to be made).
[b]From Sprague and Kalachnik [1991] and Sprague et al. [1989].
[c]From Bodfish et al. [1997].

United States District Court class action lawsuit agreement. Items are scored based on a 0 (not present) to 4 (severe) scoring system modified from the DOTES [National Institute of Mental Health, 1985b]. Table 6 presents MOSES items because the original source material may be difficult to locate and because the scale is referenced to a fair degree in the MRDD literature [Lewis et al., 1996; Matson et al., 1998; Wilson et al., 1998]. It should be noted that the scale has been altered several times over the years. Table 6 presents the updated items.

The Dyskinesia Identification System Condensed User Scale (DISCUS) [Sprague and Kalachnik, 1991; Sprague et al., 1989] is a 15-item rating scale specific to TD and organized by seven body areas. The Akathisia Rating Scale (ARMS) [Bodfish et al., 1997] is a 10-item rating scale specific to akathisia. Table 7 presents the items for both of these scales. TD and akathisia are primarily associated with antipsychotic medication. Although the Abnormal Involuntary Movement Scale may be used to check clients for TD, the DISCUS has extensive psychometric data in relation to individuals with MRDD, a clinical indicator score (total score of 5 or above), and a training program [Kalachnik et al., 1991]. The ARMS reports psychometric data and a cutoff score for individuals with MRDD (total score of 4 or more based on items 1–7 because items 8–10 were difficult to assess with many individuals).

To summarize, there are a wide variety of side effect rating scales available to conduct systematic side effect surveillance in individuals with MRDD. As can quickly be ascertained from Table 5, side effect-specific scales predominate based on measurement of movement disorders such as TD, akathisia, and other extrapyramidal side effects. In most cases, the

Table 8. Adverse Drug Reaction Causation Questions Organized by Areas

Scientific basis

1. Do professional references or reports indicate that the side effect is associated with the drug or a drug interaction? (Yes)

Clinical associations

2. Did the side effect occur or worsen after the start of the drug or a dose increase? (Yes)
3. Did a dose decrease or discontinuation of the drug improve or stop the side effect? (Yes)
4. Did a dose increase of the drug exacerbate the side effect? (Yes)
5. Did a known contractive or auxiliary drug improve the side effect? (Yes)

Laboratory value associations

6. Are blood levels or other laboratory values of the drug high, toxic, or at inappropriate levels? (Yes)

History

7. Does the person have a history of the side effect with this drug or with drugs from the same category? (Yes)

Alternative explanations

8. Was there a significant change of a health, medical, or environmental variable at the time of the side effect that explains the "apparent" side effect? (No)
9. Does the side effect occur or worsen when another medication not associated with the side effect or interaction is given? (No)

provider should select a comprehensive scale and, in cases of antipsychotic medication, also use a TD scale. Other specialized scales can be reserved for specific inquiry in relation to a particular side effect if indicated by a comprehensive scale's items, specific inquiry during periods of high probability or medication adjustment (e.g., an EPSE scale during the first 6 months of antipsychotic therapy), differentiation as to what a confusing set of signs may represent, and the effect of changes made in relation to a specific actual or hypothesized side effect.

METHODS TO DETERMINE THE PROBABILITY OF SIDE EFFECTS

Unfortunately, there is no hard and fast method to ascertain whether clinical manifestations spontaneously reported or detected by a side effects rating scale are indeed side effects. Many clients display signs and symptoms from other conditions or from an underlying behavioral or mental state. People receiving placebos can report side effects, and even healthy people complain about symptoms such as fatigue, sleepiness, and inability to concentrate [Goldman et al., 1995, 1996]. As a result, agreement between professionals is less than perfect as to the cause of clinical manifestations. In one widely referenced study, three clinical pharmacologists were asked to review standardized case data and determine whether 60 hospitalizations were caused by accidental poisoning, suicide attempt, noncompliance, alcohol, recreational drugs, or side effects [Karch et al., 1976]. Excluding disagreements pertaining to the degree of certainty assigned to a cause, agreement between the three occurred in 68% of cases. Agreement between individual pharmacologists and attending physicians was 71%. In another study, the agreement between physicians as to the certainty (e.g., definite, probable, possible, unlikely) that suspected side effects cases presented in a standard format represented a side effect varied between 33% and 53% [Leventhal et al., 1979].

The likelihood of a side effect is based on questions in five basic domains. A simple checklist of common questions to ask in relation to these domains is presented for day-to-day use in Table 8. Table 9 presents the two major schemas used to define the degree of certainty that a clinical manifestation is a side effect [Karch and Lasagna, 1975; Edwards and Biriell, 1994].

There are two widely recognized formal numerical methods available to determine ADR probability. The first is the ADR Probability Scale [Naranjo et al., 1981], which is presented in Table 10. The second is the detailed 57-item ADR Questionnaire [Kramer et al., 1979; Hutchinson et al., 1979], which is also referred to as the Kramer ADR Questionnaire [Mahoney and Miller, 1991]. The Kramer is designed along the lines of an algorithm and is not presented here because of its length. Like the 600-item plus Adverse Drug Detection Scale (ADRDS) [Corso et al., 1992], the Kramer is not as complex as first appears because many items are skipped, depending on the answer provided within the algorithm.

To summarize, the intent of side effect probability methods is not to replace prescriber judgment or to diagnose a side effect. It is not necessary to apply these methods to every clinical case, especially for more frequently encountered, expected, and obvious side effects. However, a formal methodology is available to help analyze a confusing situation and answer the first half of the ultimate question, "What do these clinical manifestations represent, and what do we do about them?" The methods may also be useful for psychopharmacologic drug research studies. In relation to the second half of the above question, there are seven basic possibilities: (1) no action, (2) dose reduction, (3) drug discontinuation, (4) contractive/auxiliary drug, (5) drug hold, (6) drug change, and (7) increased surveillance or further laboratory or other tests or data.

STUDIES OF SIDE EFFECTS IN INDIVIDUALS WITH MRDD

Unfortunately, there are no studies that address how often side effects occur in individuals with MRDD, what percent of these side effects lead to hospitalization, and what percent of these side effects are related to psychopharmacologic medication.

Existing studies and reports with individuals with MRDD address specific psychopharmacologic medications, specific antiepileptic medications, or a specific side effect. These studies suggest that side effects in this population are not uncommon. For example, Pary [1991] found that 10 of 15 (67%) of individuals treated with lithium and seen during a 58-week period at an outpatient clinic displayed side effects such as tremor, gastrointestinal irritation or bleeding, excessive sedation, and excessive thirst and polyuria. Friedman et al. [1992] found that 4 of 20 (20%) individuals treated with carbamazepine for behavioral or psychiatric disorders displayed behavioral side effects ranging from irritability to mania compared to 0 of 21 individuals treated for an isolated seizure disorder. Branford et al. [1998] reported that side effects such as vomiting, increased agitation, excessive drowsiness, and insomnia led to the discontinuation of selective serotonin reuptake inhibitors in 13 of 37 (35%) of individuals. Cook et al. [1992] reported that 3 of 16 (19%) individuals treated with fluoxetine had side effects such as restlessness, hyperactivity, agitation, decreased appetite, or insomnia, which significantly interfered with their function. Gualtieri et al. [1986] reported transitory physiological withdrawal effects when neuroleptics were discontinued for 8 of 38 (21%) individuals and acute behavior deterioration that lasted up to 16 weeks for 9 of 38 (24%) individuals. Several studies have found that the percentage of TD in individuals with MRDD ranges from 18 to 40%, depending on whether point prevalence or antipsychotic reduction procedures were involved [Bodfish et al., 1996;

Table 9. Adverse Drug Reaction Probability Level Definitions

	Description
Karch and Lasagna [1975]	
Definite:	A reaction that follows a reasonable temporal sequence from administration of the drug or in which the drug level has been established in body fluids or tissues *and* follows a known response pattern to the suspected drug *and* is confirmed by improvement on stopping the drug (dechallenge) *and* confirmed by reappearance of the reaction on repeated exposure (rechallenge)
Probable:	A reaction that follows a reasonable temporal sequence from administration of the drug *and* follows a known response pattern to the suspected drug *and* is confirmed by dechallenge *and* cannot be reasonably explained by the known characteristics of the patient's clinical state
Possible:	A reaction that follows a reasonable temporal sequence from administration of the drug *and* follows a known response to the suspected drug *but* could have been produced by the patient's clinical state or other modes of therapy administered to the patient
Conditional:	A reaction that follows a reasonable temporal sequence from administration of the drug *and* does not follow a known response pattern to the suspected drug *but* cannot be reasonably explained by the known characteristics of the patient's clinical state. (Note: this category is intended for temporary classification and to allow reclassification as more information becomes available)
Doubtful:	Any reaction that does not meet the criteria above
WHO [Edwards and Birtiell, 1994, p. 95]	
	Description
Certain:	"A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to drug administration, and which cannot be explained by concurrent disease or other chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary."
Probable/likely:	"A clinical event, including laboratory test abnormality, with a reasonable time sequence to the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge is not required to fulfill this definition."
Possible:	"A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear."
Unlikely:	"A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations."
Conditional/Unclassified:	"A clinical event, including laboratory test abnormality, reported as an adverse reaction, about which more data are essential for a proper assessment or the additional data are under examination."
Unassessable/Unclassifiable	"A report suggesting an adverse reaction which cannot be judged because information is insufficient or contraindicatory, and which cannot be supplemented or verified."

Kalachnik et al., 1984; Richardson et al., 1986].

Table 10. Adverse Drug Reaction (ADR) Probability Scale*

Item	Yes	No	Don't know
1. Are there previous *conclusive* reports on this reaction?	+1	0	0
2. Did the adverse event appear after the suspected drug was administered?	+2	−1	0
3. Did the adverse reaction improve when the drug was discontinued or a *specific* antagonist was administered?	+1	0	0
4. Did the adverse reaction reappear when the drug was readministered?	+2	−1	0
5. Are there alternative causes (other than the drug) that could on their own have caused the reaction?	−1	+2	0
6. Did the reaction reappear when a placebo was given?	−1	+1	0
7. Was the drug detected in the blood (or other fluids) in concentration known to be toxic?	+1	0	0
8. Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	+1	0	0
9. Did the client have a similar reaction to the same or similar drugs in *any* previous exposure?	+1	0	0
10. Was the adverse event confirmed by any objective evidence?	+1	0	0

Total score: _____

Scoring:	
≥9:	Definite ADR
5–8:	Probable ADR
1–4:	Possible ADR
<1:	Doubtful ADR

*From Naranjo et al. [1981].

SUMMARY

The purpose of this article has been to provide information related to measuring side effects of psychopharmacologic medication when used with individuals with MRDD. Despite the alluring simplicity of the term "side effects" in day-to-day use, the ADR field is complex. Background information regarding terms and classifications, methods, assessment instruments, and probability methods have been emphasized. On a day-to-day basis, the information in this article may best be considered within the following applied paradigm: (1) detecting the clinical manifestation and determining its severity, (2) determining whether the clinical manifestation is a side effect, (3) determining whether a drug change or other action is required, and (4) determining the effect of the decision made.

Perhaps the most important point of this article is best summarized by the old adage, "There are two effects of every medication: the one we know about and the one we don't know about." Measurement for side effects attempts to convert the later half of the statement into the former so that effective action can be taken. Despite great progress in terms of newer and safer psychopharmacologic drugs, the importance of side effects measurement in relation to good client

care remains important. This is especially important for those individuals who cannot effectively verbally communicate the presence of a side effect. ■

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